Qualità della vita in pazienti anziani con glioblastoma di nuova diagnosi trattati con radioterapia ipofrazionata associata a chemioterapia concomitante e adiuvante con temozolomide

Health-Related Quality of Life in Elderly Patients With Newly Diagnosed Glioblastoma Treated With Short-Course Radiation Therapy Plus Concomitant and Adjuvant Temozolomide

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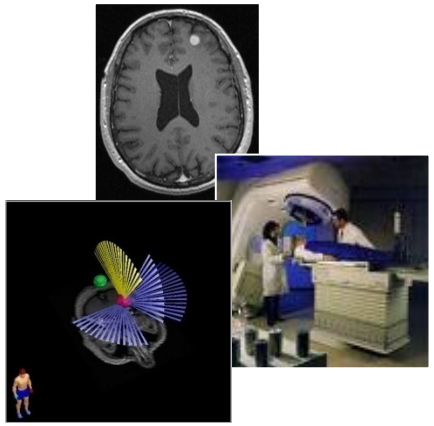


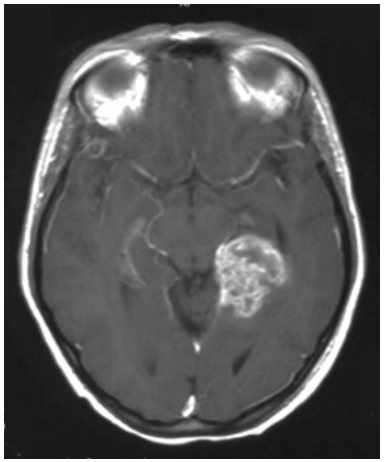
Background

Glioblastoma (GBM) is the most common primary brain tumors in adults, and approximately 22% of all patients are 70 years of age or older

Randomized and prospective studies have reported similar survival benefit in elderly patients with GBM treated with different schedules of RT or CHT, although survival is modest and the optimal management remains matter of debate

The association of standard RT and TMZ, has been advocated as an effective treatment in elderly patients with good prognostic factors, with a median survival of 8-12 months

Although combined chemoradiation and other new treatment options may improve the length of survival, benefits have to be carefully balanced against the potential toxicity and negative impact on QOL of the different treatment strategies



Aim of the study

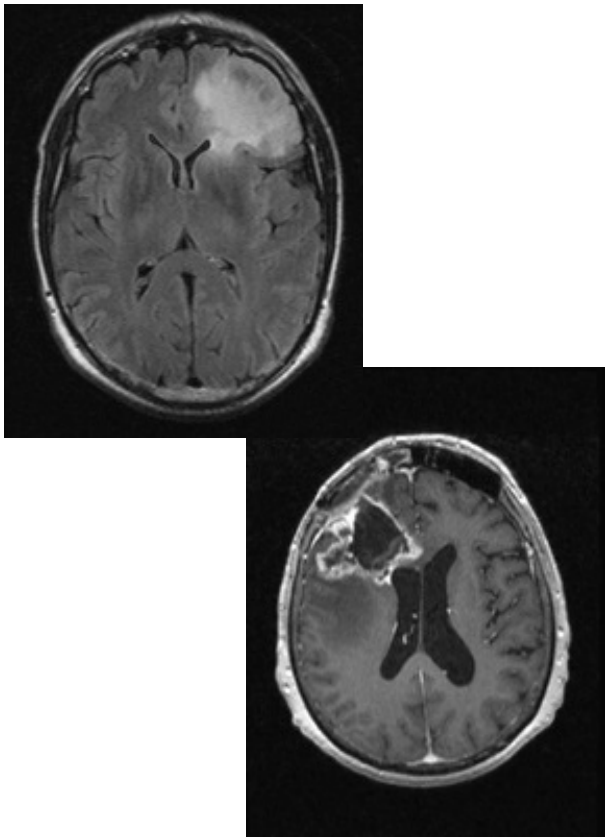
Endpoints:

OS

PFS

Toxicity

HRQOL (Health-Related Quality of Life)



Inclusion criteria:

- newly diagnosed histologically confirmed intracranial GBM
- Age ≥ 70 years
- KPS ≥ 60
- adequate bone marrow, liver, and renal function

Patients and Methods

- 65 pts between 2005 and 2010 completed the questionnaires at baseline

Treatment:

RT 40 Gy in 15 fractions plus concomitant daily TMZ, followed by adjuvant TMZ.

Concomitant chemotherapy: TMZ 75 mg/m^2, 7 days per week.

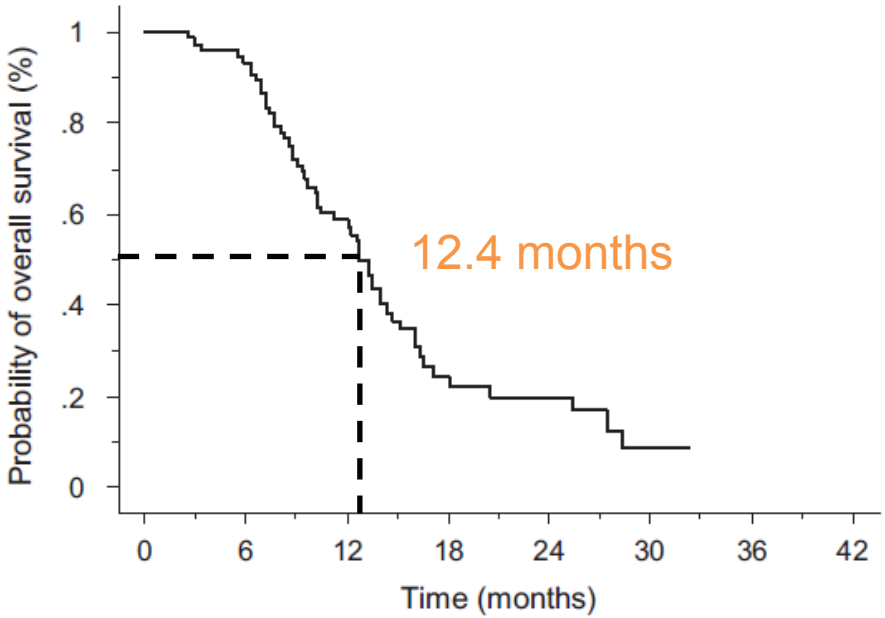
Adjuvant TMZ started 4 weeks after the end of RT for 5 days every 28 days for 12 cycles.

Dosage: 150 mg/m^2 first cycle and 200 mg/m^2 from the second cycle

Patients and Methods

Characteristic	n (%)
Age (y)	
Median	73
Range	70-81
Sex	
M	33
F	32
Karnofsky performance status	
Median	70
Range	60-100
Tumor location	
Temporal	21
Frontal	21
Parietal	16
Occipital	7
Extent of resection	
Total	10
Subtotal	22
Partial	25
Biopsy	8
MGMT methylation status	
Methylated	33
Unmethylated	32
Mini-Mental State Examination	
Median (range)	26.1 (19-30)
Missing	3
Corticosteroids at trial entry	
No	42
Yes	23
Target volumes (cm^3)	
Median GTV (range)	48.9 (14.8-192.1)
Median CTV (range)	247.6 (73.1-389.3)

Outcome: Survival



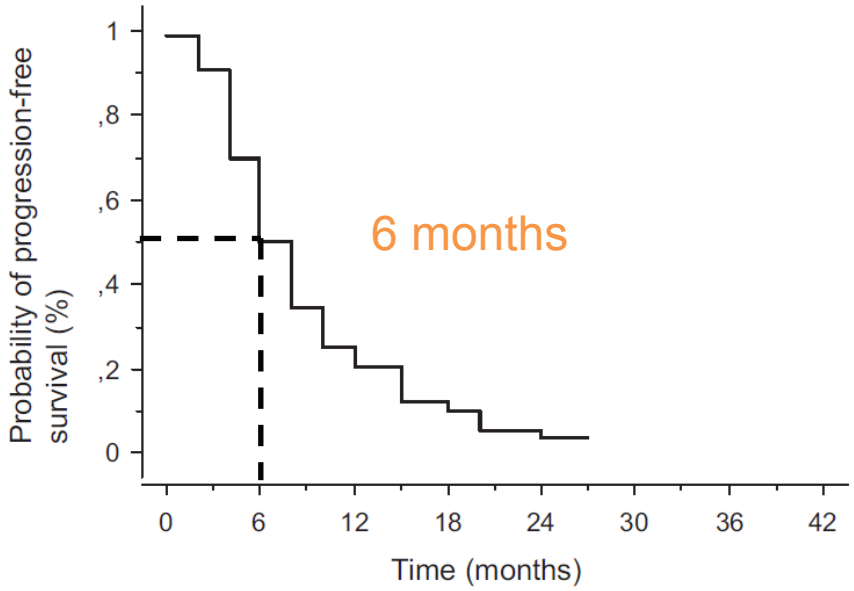
median OS 12.4 months
(95% CI, 9.9-15.0)

minimum follow-up time of 12 months.

1-year OS rate 58%
(95% CI, 45-74%)

2-year OS rate 20%
(95% CI, 6-38%)

Outcome: Progression Free Survival



median PFS 6 months
(95% CI, 4.1-8.2)

1-year PFS rate 20%
(95% CI, 9-34%)

2-year PFS rate 5%
(95% CI, 1-12%)

partial response in 22 patients.
recurrence in 61 patients:
within the treated target volume
in 53 patients (87%)
outside or distant from the
treated target volume in 8
patients (13%)

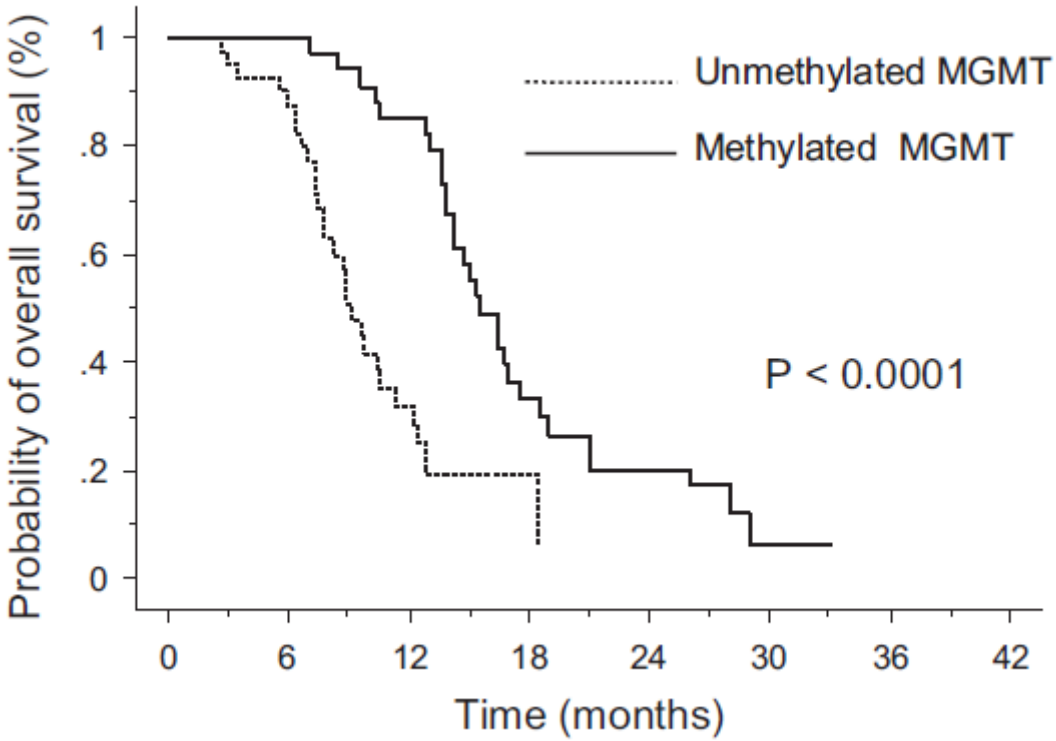
Toxicity

Event	No. of patients (%)					
	TMZ concomitant			TMZ adjuvant		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Hematologic						
Thrombocytopenia	1 (1.4)	0	0	6 (8)	8 (11)	2 (3)
Anemia				2 (3)	2 (3)	
Neutropenia	1 (1.4)	0	0	2 (3)	3 (4)	0
Lymphocytopenia	11 (15)	3 (4)	0	29 (41)	14 (20)	2 (3)
Nonhematologic						
Nausea/vomiting	0	0	0	8 (11)	0	0
Dermatologic/skin	1 (1.4)	0	0	2 (3)	0	0
Neurologic	4 (5)	0	0	2 (3)	1 (1.4)	0
Fatigue	6 (8)	1 (1.4)	0	9 (12)	3 (4)	0

Prognostic factors

Variable	Median survival time (mo)	Univariate analysis p value	Multivariate analysis	
			Hazard ratio (95% CI)	p value
Sex		0.6		
M	13.5			
F	14.7			
Age (y)		0.2		
<75	12.7			
≥75	11.4			
KPS		0.001	0.45 (0.2–0.86)	0.02
≤70	10.9			
>70	14.6			
Extent of resection		0.02	0.6 (0.34–1.1)	0.1
Total/subtotal	14,8			
Partial/biopsy	10.5			
MGMT methylation status		<0.0001	0.29 (0.16–0.52)	0.0001
Methylated	15.8			
Unmethylated	8.8			
RPA class		0.0001		
IV	14.8			
V	11.3			
VI	7.8			

MGMT methylation status



8.8 months

15.8 months

The 1-year and 2-year OS rates were 83% and 20% in methylated tumors, and 32% and 0% in unmethylated tumors

MGMT methylation status was the only factor associated with significantly better PFS (p = 0.001)

The median PFS was 10 months in methylated tumors and 4 months in unmethylated tumors (p = 0.0001)

HRQOL measurement

The HRQOL was assessed by:

- EORTC Quality of Life Questionnaire Core-30 (**QLQ-C30**, version 3)
- EORTC Quality of Life Questionnaire Brain Cancer Module (**QLQ-BN20**)

The patients completed the EORTC questionnaires:

- immediately before RT
- 4 weeks after RT (immediately before the start of chemotherapy)
- every 8 weeks during the treatment until disease progression

HRQOL measurement

The **QLQ-C30** questionnaire comprises:

- 5 function scales (physical, role, emotional, cognitive, and social)
- 3 symptom scales (fatigue, nausea and vomiting, and pain)
- 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, and financial effect of treatment)
- global QOL

The **QLQ-BN20** contains 20 items grouped into:

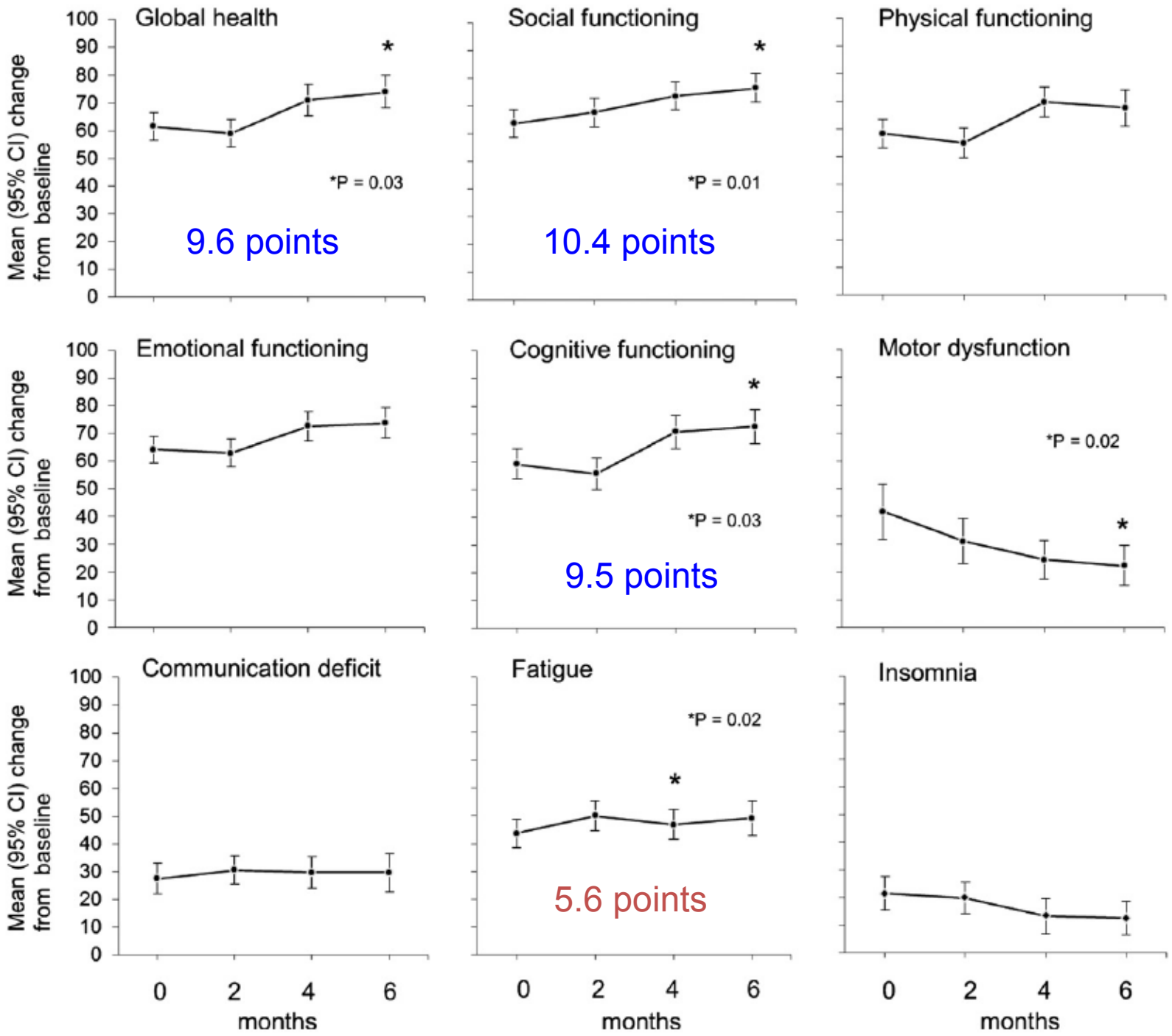
- 4 domains (future uncertainty, visual disorder, communication deficit, and motor dysfunction)
- 7 single items (headache, seizure, drowsiness,hair loss, itching, weakness of both legs, and difficulty controlling bladder function)

All raw scores were converted to lie in a range between 0 and 100

Baseline quality of life scores

- mean baseline scores for the 9 preselected domains and some additional domains of interest
- the Physical functioning and Cognitive functioning were the most impaired at baseline

Domain	Mean	SD
Preselected domains		
Social functioning	63.6	21.2
Global QOL	61.5	20.8
Emotional functioning	64.4	19.7
Communication deficit	27.5	22.9
Fatigue	43.7	20.8
Insomnia	21.6	25.3
Motor dysfunction	41.7	25.3
Physical functioning	58.4	22.1
Cognitive functioning	59.3	22.8
Other domains		
Role functioning	52.2	26.3
Drowsiness	39.8	22.7
Future uncertainty	40.8	20.4
Nausea and vomiting	2.9	9.1
Loss of appetite	13.2	16.3
Constipation	14.1	19.4
Pain	12.1	15.3


Global health
Social functioning
Physical functioning
Emotional functioning
Cognitive functioning
Motor dysfunction
Communication deficit
Fatigue
Insomnia
Mean (95% CI) change from baseline
100
90
80
70
60
50
40
30
20
10
0
*P = 0.03
*P = 0.01
*P = 0.02
*P = 0.03
*P = 0.02
*
9.6 points
10.4 points
9.5 points
5.6 points
0
2
4
6
months

Proportion of patients who reported improvement of 10 in preselected HRQOL scores

Domain	No. eligible	No. responding (%)	Duration of response, mo, mean ± SD
Social functioning	60	16 (27)	4.4 ± 2.7
Global QOL	62	17 (27)	6.0 ± 3.2
Emotional functioning	63	10 (16)	5.8 ± 2.8
Communication deficit	54	9 (14)	5.8 ± 3.1
Fatigue	65	6 (9)	5.2 ± 2.4
Insomnia	34	10 (29)	6.0 ± 3.9
Motor dysfunction	51	12 (18)	5.6 ± 2.3
Physical functioning	63	13 (20)	4.8 ± 3.0
Cognitive functioning	63	10 (16)	5.5 ± 2.4

Outcome: MMSE scores

Changes over time in MMSE scores

Parameter	Baseline before RT	1st follow-up 4 wk	2nd follow-up 12 wk	3rd follow-up 24 wk	4th follow-up 48 wk
Evaluable patients	71	62	49	32	12
Mean score	26.1	26.3	26.9	27.5	27.5
SD	2.9	2.8	1.7	1.4	1.6
Range	21-30	21-30	23-30	24-30	24-30
Improved (n)		3	5	4	2
Worsened (n)		2	4	2	1
Unchanged (n)		49	31	18	5
Missing	6	8	9	8	4

The average pretreatment MMSE was 26.1

- After 6 months from baseline, MMSE was available in 24 patients.
- MMSE score improved in 4 (14%) patients
- Remained stable in 18 (79%).
- In 2 (7%) patients worsened, most frequently on recall and serial 7.

- After 12 months, MMSE score improved in 2 (25%), worsened in 1 (12%), and was unchanged in 5 (63%) patients
- Overall, during a 12-month follow-up period, MMSE score improved or remained stable in 89% of patients free of disease progression.
- A significant decrease of MMSE score occurred in 11% of patients without radiologic evidence of progression.

Conclusions

- In conclusion, a short course of RT in combination with TMZ was of benefit in elderly patients with GBM. The treatment was associated with improvement in, or at least preservation of, important HRQOL domains until the time of disease progression.

- Further studies are required to compare the potential advantages of combined chemoradiation over RT or chemotherapy alone in this population.

Thank you!